

# Synthesis of Novel Cyclic Oligosaccharides: $\beta$ -1,6-Thio-Linked Cycloglucopyranosides

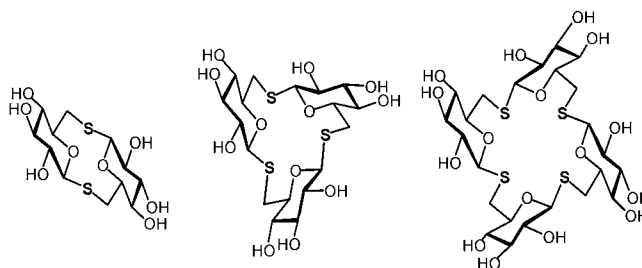
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## ABSTRACT



A protocol for the synthesis of novel cyclic  $\beta$ -1,6-S-linked glucopyranosides is developed. The key intermediate is a linear thiooligosaccharide bearing an iodo group at C-6 of the nonreducing sugar and a thioacetyl group at the anomeric center of the reducing end sugar. The crucial macrocyclization step was achieved through base-promoted intramolecular  $S_N2$  glycosylation in remarkably high yields (92–95%) and with well-controlled stereochemistry.

The ability of natural cyclic sugars, especially the cyclodextrins (CDs), to form unique inclusion complexes<sup>1–5</sup> with a large variety of substances continues to stimulate interest in the enzymatic and chemical synthesis of cyclic oligosaccharides. Organic synthesis allows the construction of unnatural cyclic oligosaccharides that can incorporate different inter-glycosidic linkages and varied numbers and types of monosaccharide units, not only the homopolymeric  $\alpha$ -1,4-linked D-glucopyranoside residues found in the native CD family. Numerous synthetic cyclic oligosaccharides have been reported.<sup>6–9</sup> However, no reports have appeared de-

scribing cyclic oligosaccharides with exclusively thio glycosidic linkages. Thiooligosaccharides, which contain sulfur atoms in their glycosidic linkage, have been extensively studied in glycobiology as tools for understanding the crucial interaction between oligosaccharides and glycosidases.<sup>10</sup> We envisaged that cyclic thiooligosaccharides would be not only more stable toward acidic hydrolysis or enzymatic degradation than their O-linked counterparts but also more interesting since the sulfur atoms in the ring system may bind selectively to certain metal ions. This prompted us to synthesize a series of cyclic  $\beta$ -1,6-thio-linked D-glucopyranosides containing two, three, and four sugar residues.

Our strategy for the synthesis of the target molecules started with the stepwise preparation of linear thiooligosaccharides by iterative glycosyl coupling between a 6-iodo monosaccharide and an anomeric thiolate generated from a 1-thioacetyl glucose residue (Scheme 1). The final coupling

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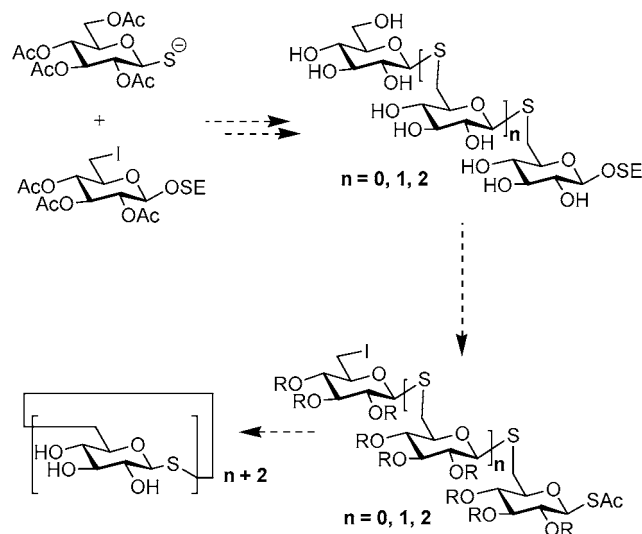
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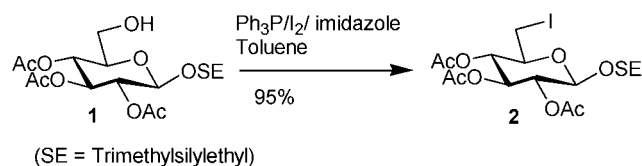
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**Scheme 1.** Synthetic Strategy

was followed by functionalization of both ends of the linear thiooligosaccharide, again with primary iodo and anomeric thioacetyl groups. Under nucleophilic and basic conditions, the 1-thiolate was generated in situ and then the intramolecular cycloglycosylation was executed to give the desired product.

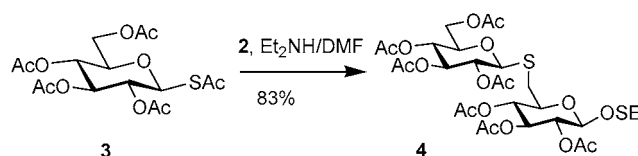
Many synthetic routes are available to establish linear 1,6-linked thiooligosaccharides. The most effective method is the reaction of 6-deoxy-6-iodo glycoside derivatives with 1-thiolate anion.<sup>11</sup> Trimethylsilylethyl (SE) glycoside **2** was chosen as a building block because SE is an excellent stable anomeric-blocking group and is amenable to transformation into many other functional groups under mild conditions.<sup>12</sup>

Building block **2** was simply synthesized by iodination of 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl- $\beta$ -D-glucopyranoside<sup>13</sup> with  $\text{Ph}_3\text{P}/\text{Imidazole}/\text{I}_2$  in toluene<sup>14</sup> in 95% yield. (Scheme 2)

**Scheme 2.** Synthesis of Building Block **2**

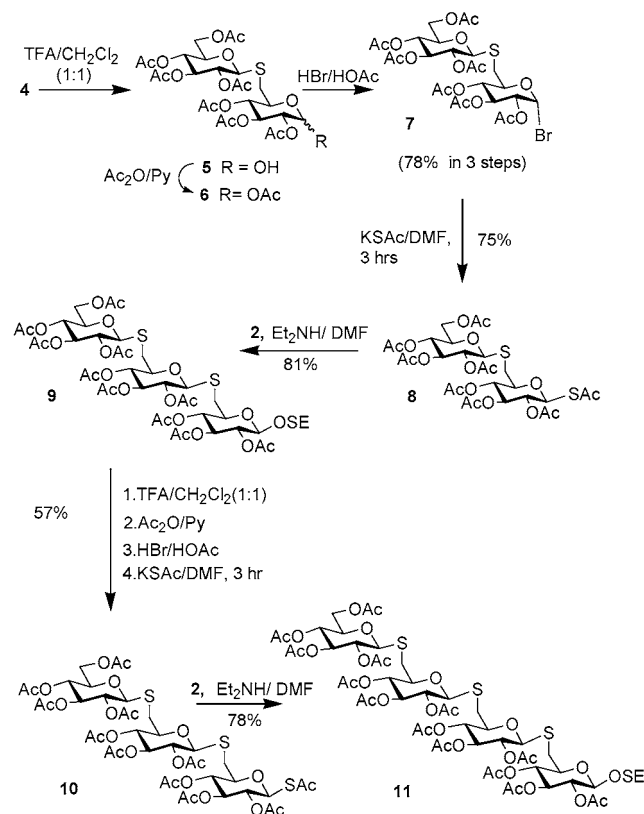
The thioglycosyl coupling was achieved by adding diethylamine into a mixture of thioacetate **3** and iodide **2** in DMF solution.<sup>15</sup> The thiolate anion was generated in situ by

the action of diethylamine, and the 1,6-thio-glycosyl linkage then readily formed in 83% yield via nucleophilic displacement of the 6-iodo group of **2** in one pot (Scheme 3).

**Scheme 3.** Coupling Step and Synthesis of *S*-Linked Disaccharide

Reaction temperature proved crucial for achieving high  $\beta$ -selectivity. When reaction was carried out at room temperature, a 1:2 mixture of  $\alpha$ - and  $\beta$ -anomers was obtained. Stereoselectivity of coupling reaction was improved ( $\alpha:\beta = 1:20$ ) when it was performed below 0 °C.

To prepare the longer linear thiooligosaccharides, the OSE group in disaccharide **4** is considered to convert into a 1-thioacetate for the next round of coupling with **2** (Scheme 4). Attempts to convert **4** to the glycosyl chloride

**Scheme 4.** Synthesis of Linear Thiooligosaccharides

( $\text{Cl}_2\text{CHOMe}/\text{ZnCl}_2$  at -40 °C) or the glycosyl acetate ( $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{Ac}_2\text{O}$ ) resulted in cleavage of the interglycosidic thio linkage. The desired transformation was finally achieved in four steps: removal of SE by  $\text{TFA}/\text{CH}_2\text{Cl}_2$  (1:1) (**4**  $\rightarrow$  **5**),

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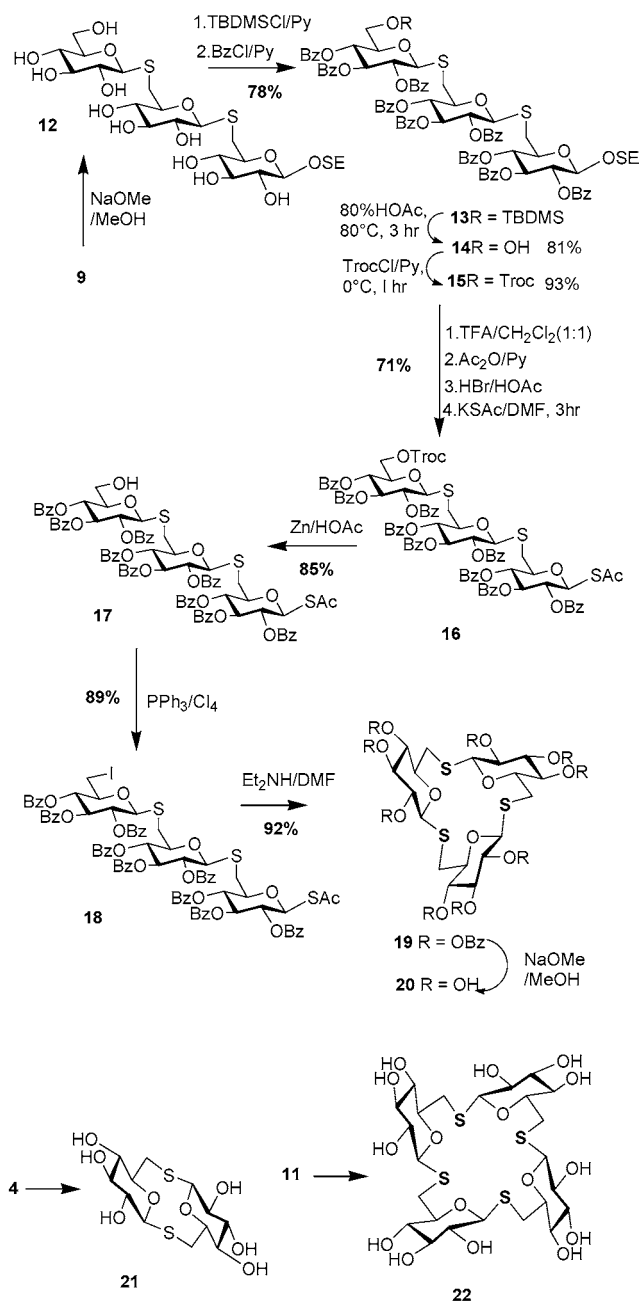
acetylation of hemiacetal **5** with pyridine/Ac<sub>2</sub>O (**5** → **6**), bromination of acetate **6**, and reaction of the bromide **7** with potassium thioacetate in DMF. The disaccharide  $\beta$ -thioacetate **8** was prepared in an overall yield of 59% from SE glycoside **4**. The subsequent coupling between **8** and **2** generated the trisaccharide **9** in 81% yield. Similarly, tetrasaccharide **11** was prepared (78%) from the trisaccharide thioacetate **10**.

With linear thiooligosaccharides **4**, **9**, and **11** in hand, we focused our attention on accomplishing the crucial macrocyclization step. Encouraged by the efficient condensation between 6-iodo and anomeric thioacetates in the presence of Et<sub>2</sub>NH, we selected this combination for the intramolecular cyclization. The synthesis of cyclic trisaccharide **20** is shown in detail in Scheme 5. Identical procedures were used for the conversion of **4** to cyclic disaccharide **21** and **11** to cyclic tetrasaccharide **22**.

Compound **9** was de-*O*-acetylated to **12**, where the primary OH was protected as its TBDMS ether prior to *O*-benzoylation to provide **13** (78%). Since conversion of the anomeric OSE group into a 1-thioacetyl group would require acid conditions, the TBDMS group was replaced with a trichloroethoxy carbonyl (Troc) group, most widely employed for protecting amino groups.<sup>16</sup> Removal of the TBDMS group in **13** (TFA, 81%) and introduction of the Troc group gave **15** (93%). The Troc group survived the acidic conditions required to transform the SE glycoside **15** into the 1-thioacetyl derivative **16**.<sup>17</sup> Attempts to shorten this reaction sequence by directly installing a primary Troc group in **12** failed.

The Troc protecting group was next reductively cleaved by Zn/HOAc (85%). Iodination of **17** using triphenylphosphine and carbon tetraiodide<sup>18</sup> gave the desired bifunctionalized linear trisaccharide **18** in 89% yield, which was dissolved in DMF. The intramolecular cyclization reaction occurred upon addition of excess Et<sub>2</sub>NH, and the reaction was complete within 3 h, generating the fully benzoylated cyclic  $\beta$ -1,6-thio-linked trisaccharide **19** in 92% yield. No  $\alpha$ -anomer was isolated. Surprisingly, the procedure resulted only in an intramolecularly cyclized product even when carried out at a high concentration (0.1 M) of the solution of **18**. No linear dimers or trimers were detected by MS. Zemplén debenzoylation provided the fully deprotected cyclic sugar **20**. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the cyclic compound **20** confirmed the symmetry. Compound **20** gave rise to one set of glycopyranoside signals, corresponding to the repeating monomer unit. Connectivities were established by COSY NMR spectroscopy, and the molecular composition was confirmed by high-resolution EI-MS. Using identical procedures, the cyclic disaccharide **21** and tetrasaccharide **22** were synthesized starting from the linear saccharides **4** and **11**, respectively. Both cyclization steps were achieved in high yields (92% and 95%, respectively), and

**Scheme 5.** Synthesis of Cyclic  $\beta$ -1,6-Thio-Linked Oligosaccharides



again only intramolecular cyclized products were obtained as we observed in the synthesis of the cyclic trisaccharide **20**.

In conclusion, we have described the synthesis of a novel class of cyclic oligosaccharide, cyclic 1,6-*S*-linked glucopyranosides. We expect that this method can be applied in the synthesis of cyclic thiooligosaccharides with larger ring sizes. Our successful preparation of **20**–**22** broadens the family of synthetic cyclic oligosaccharides. Currently we are studying the 3-D structure of these novel cyclic compounds and are investigating their complexation with transition metals, since the structure of these compounds is essentially

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that of crown ethers differing in the number of thioglucopyranoside rings.

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**Supporting Information Available:** Detailed experimental procedures and spectral data for all described compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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